BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.149 Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)

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Related Policies:

2.04.02 - Germline Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2)
2.04.08 - Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
2.04.126 - Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk (CHEK2, ATM, and BARD1)
2.04.128 - Genetic Testing for Fanconi Anemia
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)

Description

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It is estimated that approximately 20% of women presenting for assessment for hereditary ovarian cancer (OC) risk have a variant in a gene that increases the risk of cancer. *BRIP1*, *RAD51C*, *RAD51D, NBN,* and mismatch repair genes are estimated to contribute to 10% of hereditary OC cases. Approximately 60% of the familial relative risk in OC is unexplained. Risk for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* carriers is increased approximately 3- to 19-fold, 3- to 6-fold, 5- to 12-fold, and 2- to 3.5-fold respectively. Risk estimates may be higher in patients with a family history of OC or a family history of a specific gene variant.

OBJECTIVE

The objective of this evidence review is to determine whether *germline* (not somatic) testing for *BRIP1*, *RAD51C, RAD51D,* and *NBN* variants in women with diagnosed ovarian cancer or undiagnosed women in a family at risk of hereditary ovarian cancer improves the net health outcome.

POLICY STATEMENT

Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk assessment in adults may be considered **medically necessary** when the following criteria are met:

- The individual has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; AND
    - The individual has not previously been tested for these gene variants; AND
    - The individual is thought to be the most informative member of a family (proband) to have genetic testing (see Policy Guidelines); AND
    - The individual has closely related (first- and/or second-degree) relatives who are considering genetic testing for these gene variants to inform prophylactic decision-making or who have test results that cannot be fully interpreted without testing an affected relative; OR
- The individual has not been diagnosed with epithelial ovarian cancer; AND
    - The individual has any blood relative with a known pathogenic/likely pathogenic germline *BRIP1*, *RAD51C*, or *RAD51D* variant; OR
    - The individual has a first- or second-degree relative diagnosed with ovarian cancer.[a]

Testing for germline *NBN* variants for ovarian cancer risk assessment in adults is considered **investigational**.

Testing for germline *BRIP1*, *RAD51C*, *RAD51D,* and *NBN* variants in individuals diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to guide treatment of the diagnosed individual is considered **investigational**.

Testing for germline *BRIP1*, *RAD51C*, and *RAD51D* variants for ovarian cancer risk in adults who do not meet the criteria above is considered **investigational**.

[a] For familial assessment, first- and second-degree relatives are blood relatives on the same side of the family (maternal or paternal):

- First-degree relatives: parents, siblings, and children.
- Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.

POLICY GUIDELINES

Recommended Genetic Testing Strategies

Individuals who meet criteria for *germline* (not somatic) genetic testing as outlined in the policy statements should be tested for variants in *BRIP1*, *RAD51C*, and *RAD51D*. Recommended strategies are listed below.

- In individuals with a known familial germline *BRIP1, RAD51C, or RAD51D* variant, targeted testing for the specific variant is recommended.
- In individuals with an unknown familial germline *BRIP1, RAD51C, or RAD51D* variant:
    - To identify clinically significant variants, the National Comprehensive Cancer Network (NCCN) advises testing a relative who has early-onset disease, bilateral disease, or multiple primaries, because that individual has the highest likelihood of obtaining an informative, positive test result. This individual, the first-affected individual in a family who brings a genetic disorder to the attention of the medical community, is commonly referred to as the proband.
    - Testing undiagnosed, at-risk family members when a diagnosed relative is unavailable for testing, is unwilling to undergo testing, or is unwilling to share genetic testing results, should still be considered. However, indeterminate genetic testing results may be poorly understood by family members (Himes et al [2019]; PMID 31199558). Therefore, significant limitations of interpreting test results, including uninformative negative results or non-actionable variants of unknown significance (VUS), should be discussed.

Germline genetic testing for *BRCA1, BRCA2*, and *PALB2* is addressed separately in evidence review 2.04.02.

This policy applies to testing for ovarian cancer risk assessment, and does not address testing for autosomal recessive conditions associated with *BRIP1, RAD51C, or NBN.* Germline testing for Fanconi Anemia addressed separately in evidence review 2.04.128.

Testing for *ATM* in the context of hereditary breast cancer is addressed separately in evidence review 2.04.126. NCCN recommends that *ATM* carriers at risk for epithelial ovarian cancer should be managed based on family history alone.

Testing Undiagnosed, At-Risk Individuals

In unaffected (ie, undiagnosed), at-risk family members of potential *BRIP1, RAD51C, or RAD51D* variant families, most test results will be negative and uninformative. Therefore, it is strongly recommended that an *affected* (ie, diagnosed) family member be tested first whenever possible to adequately interpret the test. Should a causative variant be found in an affected family member(s), DNA from an *unaffected* family member can be tested specifically for the same variant of the affected family member without having to sequence the entire gene. Interpreting test results for an *unaffected* family member without knowing the genetic status of the family may be possible in the case of a positive result for an established disease-associated variant but leads to difficulties in interpreting uninformative negative test results or VUS because the possibility of a causative variant is not ruled out (Himes et al [2019]; PMID 31199558). Non-actionable VUS are highly prevalent with multi-gene testing, which may be avoided with targeted testing for a known familial variant (Tung et al [2016]; PMID: 27296296).

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society"s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign" - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. *BRIP1, RAD51C, RAD51D,* and *NBN* testing are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories offering to test and voluntarily list are available through the National Center for Biotechnology Genetic Testing Registry. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Customized next-generation sequencing panels provide simultaneous analysis of multiple cancer predisposition genes, and typically include both moderate- and high-penetrance genes.

Myriad Genetic Laboratories offers the myRisk Hereditary Cancer multi-gene panel test which includes 35 genes. Testing for OC risk includes analysis of *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, EPCAM, TP53, STK11, PALB2*, *BRIP1*, *RAD51C*, and *RAD51D* genes.

Ambry Genetics offers the BRCANext-Expanded panel which includes 23 genes associated with risk of gynecologic cancer, including *BRIP1*, *RAD51C*, and *RAD51D.* Testing for *NBN* is also included in this panel.

RATIONALE

Summary of Evidence

For individuals without diagnosed epithelial ovarian cancer (EOC) and in a family at risk of developing EOC who receive germline genetic testing for genes associated with hereditary ovarian cancer (OC) (ie, *BRIP1*, *RAD51C*, and *RAD51D*), the evidence includes studies of clinical validity and studies of OC risk, including meta-analyses. Relevant outcomes are overall survival (OS), disease-specific survival, and test validity. Evidence supporting clinical validity was obtained from numerous studies reporting relative risk (RR) or odds ratios (OR) and 4 studies provided penetrance estimates. Study designs included family-based case-control and population- or multicenter-based case-control. The number of pathogenic (P)/likely pathogenic (LP) variants identified in association studies ranged from 10 to 36, 11 to 44, and 8 to 13 for *BRIP1*, *RAD51C*, and *RAD51D*, respectively. The RR for OC associated with *BRIP1* ranged from 3 to 19, with population-based studied reporting the 2 highest and lowest values. The RR for OC associated with *RAD51C* ranged from 3 to 6, with a family-based study reporting the highest value. The RR for OC associated with *RAD51D* ranged from 5 to 12, with family- and population-based studies reporting the highest values. Evidence of preventative interventions in women with *BRIP1*, *RAD51C*, and

RAD51D variants is indirect, relying on studies of high-risk women and *BRCA* carriers. These interventions include chemoprevention with oral contraceptives and risk-reducing oophorectomy and risk-reducing salpingo-oophorectomy (RRSO). Given the penetrance of *BRIP1*, *RAD51C*, and *RAD51D* variants, the outcomes following risk-reducing oophorectomy and RRSO examined in women with a family history consistent with hereditary OC (including *BRCA1* and *BRCA2* carriers) can be applied to women with *BRIP1*, *RAD51C*, and *RAD51D* variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary OC who would consider risk-reducing interventions, identifying a *BRIP1*, *RAD51C*, or *RAD51D* variant provides a more precise estimated risk of developing OC compared to family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. Additionally, RRSO may provide an opportunity for occult gynecologic cancer detection in high-risk *BRCA*-negative women. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who receive germline genetic testing for *NBN* gene variants, the evidence includes studies of clinical validity and studies of OC risk, including a meta-analysis. Relevant outcomes are OS, disease-specific survival, and test validity. *NBN* variants have been associated with a 2- to 3.5-fold increased risk of OC across studies. However, a significantly increased frequency of *NBN* mutations has not been consistently observed in cases versus controls and penetrance estimates have not been reported. Accordingly, national guidelines have not recommended risk-reducing interventions for *NBN* carriers at this time due to insufficient data to define risk and recommend managing these individuals based on family history alone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-degree relative(s) with a personal history of EOC for genes associated with hereditary OC (ie, *BRIP1*, *RAD51C*, and *RAD51D*) to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, the evidence on the use of preventative interventions is indirect, relying on studies of at-risk women and *BRCA* carriers. Relevant outcomes are OS, disease-specific survival, and test validity. Evidence of preventative interventions in women with *BRIP1*, *RAD51C*, and *RAD51D* variants is indirect, relying on studies of high-risk women and *BRCA* carriers. Preventative interventions include chemoprevention with oral contraceptives and risk-reducing oophorectomy and RRSO. Given the penetrance of *BRIP1*, *RAD51C*, and *RAD51D* variants, the outcomes following risk-reducing oophorectomy and RRSO examined in women with a family history consistent with hereditary OC (including *BRCA1* and *BRCA2* carriers) can be applied to women with *BRIP1*, *RAD51C*, and *RAD51D* variants, with the benefit-to-risk balance affected by penetrance. In women at risk of hereditary OC who are considering prophylactic surgery, genetic testing of first- and/or second-degree relative(s) with a personal history of EOC to identify a familial *BRIP1*, *RAD51C*, or *RAD51D* germline variant provides a more precise estimated risk of developing OC compared to family history alone, and reduces the incidence of uninformative negative test results or non-actionable variants of unknown significance (VUS). Identification of and targeted testing for a known familial variant can offer women a more accurate understanding of benefits and potential harms of prophylactic surgery, and is a testing strategy supported by national guidelines. Testing a relative with early-onset disease, bilateral disease, or multiple primaries is recommended, as that individual has the highest likelihood of obtaining an informative, positive test result. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-degree relative(s) with a personal history of EOC for *NBN* gene variants to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, direct evidence is lacking. Relevant outcomes are OS, disease-specific survival, and test validity. National guidelines have not recommended prophylactic surgery due to insufficient data to establish absolute risk estimates. Given that the clinical validity of *NBN* germline variant testing has not been established, a chain of evidence cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with diagnosed OC who receive germline genetic testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* gene variants to guide treatment decisions in the individual with diagnosed EOC, the evidence includes studies of variant prevalence and studies of OC risk. Relevant outcomes are OS, disease-specific survival, and test validity. Direct evidence for the clinical utility of genetic testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants in individuals with OC was not identified. Due to the standard surgical management of OC patients, the clinical utility of *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variant testing to inform therapy was reviewed. In studies evaluating homologous recombination deficiency (HRD) assays in *BRCA* wild-type patients, an overlapping therapeutic benefit was found between deficient/high loss-of-heterozygosity and proficient/low loss-of-heterozygosity tumors and results were not stratified by non-*BRCA* HRD genes. The use of *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variant status to guide maintenance and recurrence therapy continues to be elucidated in the clinical trial setting. In contrast to undiagnosed women at high familial risk of OC, women diagnosed with OC who undergo testing for *BRIP1*, *RAD51C*, *RAD51D*, and *NBN* variants do not yield clinically actionable results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Clinical Oncology

In 2020, the American Society for Clinical Oncology (ASCO) issued guidelines regarding germline and somatic tumor testing for women with epithelial ovarian cancer (EOC).[41,] A systematic review evaluating 19 systematic reviews of observational data, consensus guidelines, and randomized controlled trials informed the guideline recommendations. The ASCO Expert Panel recommends that germline sequencing of *BRCA1* and *BRCA2* be performed in the context of a multi-gene panel. This multi-gene panel should, at minimum, additionally include *RAD51C, RAD51D, BRIP1, MLH1, MSH2, MSH6, PMS2*, and *PALB2*. For women who do not carry a germline pathogenic/likely-pathogenic *BRCA1/2* mutation, somatic tumor testing for *BRCA1/2* is recommended. The guideline recommendations state that women with EOC should be offered testing at the time of diagnosis as this has implications for therapeutic decision-making.

In 2024, ASCO issued guidelines regarding selection of germline genetic testing panels in patients with cancer.[49,] They recommend genes for testing and inclusion in multigene panels for EOC. The more strongly recommended genes, which are those with a higher relative risk or are highly actionable, include: *BRCA1*, *BRCA2*, *BRIP1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D*. *ATM* is included as a less strongly recommended gene for its moderate relative risk and is less actionable.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancer (v.3.2024) review single-gene tests for *BRIP1*, *RAD51C*, and *RAD51D*.[15,] However, the inclusion of these genes in the guidelines does not imply endorsement for or against multi-gene testing for moderate-penetrance genes. Based on estimates of lifetime risk of ovarian cancer (OC) in carriers of pathogenic/likely pathogenic variants in *BRIP1*, *RAD51C*, or *RAD51D* from available studies, there appears to be sufficient evidence to justify consideration of risk-reducing salpingo-oophorectomy (RRSO). However, while the current evidence is insufficient to firmly recommend an optimal age for risk-reducing surgery, based on the limited evidence base, the guidelines recommend that a discussion regarding RRSO should be held around 45 to 50 years of age or earlier based on specific family history of an earlier onset of OC. It is also recommended that *RAD51C* and *RAD51D* germline variant carriers receive annual mammograms and to consider breast magnetic resonance imaging (MRI) with contrast starting at age 40 years. Regarding *NBN*, the guideline states that there is insufficient evidence to make any recommendations for breast MRI, RRSO, or risk-reducing mastectomy.

The NCCN guidelines on EOC (v.2.2024) provide primary treatment recommendations for patients with stage IA-IV disease.[40,] For those desiring fertility with stage IA or IB disease, unilateral and bilateral salpingo-oophorectomy with comprehensive surgical staging are recommended, respectively. For stage IA-IV patients not desiring fertility where optimal cytoreduction is likely, hysterectomy and bilateral salpingo-oophorectomy are recommended in combination with debulking as needed. For surgical candidates, germline and somatic testing is recommended following surgery. For poor surgical candidates or those with a low likelihood of optimal cytoreduction, neoadjuvant therapy is recommended with genetic risk evaluation. The guidelines note that *BRCA1/2* status may inform maintenance therapy. In the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of therapy with poly(ADP-ribose) polymerase (PARP) inhibitors.

Society of Gynecologic Oncology

In 2013, the Society of Gynecologic Oncology (SGO) issued a clinical practice statement with recommendations concerning salpingectomy for OC prevention.[50,] For women who have *BRCA1* or *BRCA2* germline mutations, counseling regarding bilateral RRSO after completion of childbearing is recommended. For women who choose to delay or forego RRSO, counseling regarding risk-reducing salpingectomy when childbearing is complete is recommended, followed by oophorectomy at a future date, although data on the safety of this approach are limited. For women who are at average, population risk of OC, risk-reducing salpingectomy should be considered with patients at the time of abdominal or pelvic surgery, hysterectomy, or in place of tubal ligation.

U.S. Preventive Services Task Force Recommendation

No U.S. Preventive Services Task Force recommendations for *BRIP1*, *RAD51C, RAD51D*, or *NBN* variant testing have been identified.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2022	Replace policy	Policy updated with literature review through July 25, 2022; references added. Evidence review and investigational policy statements added for germline NBN genetic testing. Policy title changed to: "Molecular Testing for Germline Variants Associated with Ovarian Cancer (BRIP1, RAD51C, RAD51D, NBN)."
December 2023	New policy	Policy updated with literature review through July 7, 2023; reference added. Policy statements unchanged. FEP new policy.
December 2024	Replace policy	Policy updated with literature review through June 14, 2024; reference added. Policy statements unchanged.